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TITLE: Monitoring the Response of Chemotherapy on Breast Cancer
Tumors by Photon Migration Spectroscopy

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Annual Summary (6 May 2003 - 5 May 2004)

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Molecular Characteristics of Multicorn, a New Large
Proteolytic Assembly and Potential Anti-Cancer Drug Target,
in Human Breast Cancer Cells

5. FUNDING NUMBERS

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12b. DISTRIBUTION CODE**13. ABSTRACT (Maximum 200 Words)**

Optimal management of patients with locally advanced breast cancer (LABC) remains a complex therapeutic problem. The optimal intensity and duration of the neoadjuvant chemotherapy regiment for LABC still remains controversial due to the difficulty of evaluating response to the treatment. The goal of this project is to use Photon Migration Spectroscopy (PMS) as a new modality to monitor the response of breast tumor to neoadjuvant chemotherapy. Photon Migration Spectroscopy has shown excellent sensitivity to the crucial early functional changes in breast tissue subjected to neoadjuvant chemotherapy. We have measured over 18 patients and have seen optical changes in responders and lack of optical and lack of optical changes in non-responders. We are still in process of enrolling more patients and refining the stability and reproducibility of the data collected thus far. In addition, we have defined an "Optical Index," which incorporates all the optical parameters into a single easy to understand value which better describes the response of the tumor to the neoadjuvant chemotherapy.

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Neoadjuvant chemotherapy, photomedicine, laser imaging

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INTRODUCTION

Optimal management of patients with locally advanced breast cancer (LABC) remains a complex therapeutic problem. The optimal intensity and duration of the neoadjuvant chemotherapy regiment for LABC still remains controversial due to the difficulty of evaluating response to the treatment. The goal of this project is to use Photon Migration Spectroscopy (PMS) as a new modality to monitor the response of breast tumor to neoadjuvant chemotherapy. Photon Migration Spectroscopy has shown excellent sensitivity to the crucial early functional changes in breast tissue subjected to neoadjuvant chemotherapy. We have measured over 18 patients and have seen optical changes in responders and lack of optical changes in non-responders. We are still in the process of enrolling more patients and refining the stability and reproducibility of the data collected thus far. In addition, we have defined an "Optical Index" which incorporates all the optical parameters into a single easy to understand value which better describes the response of the tumor to the neoadjuvant chemotherapy.

BODY

Statement of Work Accomplishments

SPECIFIC AIM 1: DEVELOP TRIAL PROTOCOL

1/2. Develop subject tracking system / Design Database

These tasks have been completed. (last report 2003)

SPECIFIC AIMS 2 : TRAINING

- 1. Audit Bioengineering ,Physics and Photomedicine courses on campus to enhance fundamental knowledge of Photon Migration Spectroscopy*

This task has been completed. I am still continuing to attend the Beckman Laser Institute lecture series to keep current with the new developments in the field of optics.

- 2. Rotation in Pathology department to learn slide preparation and immunohistochemical staining*

This task has been completed. (last report 2003)

3. Enrollment in Ultrasound training course

This task has been completed. As described in the last report we were fortunate and have been able to obtain a brand new TITAN portable ultrasound. I have completed a formal course on the use of the ultrasound. I am obtaining both a portable ultrasound reading and a formal Radiology department ultrasound on the patients whenever possible.

SPECIFIC AIMS 3: ENROLLMENT OF SUBJECTS

1. Start enrollment of subjects

This task continues. Thus far we have enrolled 18 subjects. Only 3 subjects (16%) have withdrawn from the study for various reasons. See **Appendix A**

2. Scheduling of subsequent measurement dates

This task continues. By analyzing the preliminary data, it was determined that the biologically more significant time for measurement is in the early part of the chemotherapy cycle (ie 2-3 weeks). This is demonstrated in all patients who responded to chemotherapy. As a result, we have been concentrating on obtaining more readings in the initial 2-3 weeks of the chemotherapy regiment.

SPECIFIC AIMS 4 : TUMOR MEASUREMENTS

1. Obtain Pre - Post Chemotherapy Photon Migration Spectroscopy measurements

This task continues. See **Appendix B** for preliminary raw Optic data and data plots
Appendix C for calculation of the OPTIC INDEX

2. Obtain Pre - Post Chemotherapy Ultrasound measurements

This task has started and continues.

SPECIFIC AIMS 5 : CORRELATION OF PMS MEASUREMENTS WITH ULTRASOUND AND HISTOLOGY DATA

1. Correlation of Ultrasound data and PMS data

This task is starting.

2. Analysis of histology data with immunohistological staining of post surgical specimens

This task is pending.

SPECIFIC AIMS 6 : FINAL ANALYSIS AND REPORT

1. Analysis of all data

This task is pending.

2. Preparation of manuscript

This task is pending.

KEY RESEARCH / CAREER ACCOMPLISHMENTS

1. Development of database for data management
2. Development of trial protocol
3. Obtaining IRB approval of protocol
4. Audit of Photomedicine / Optic courses
5. Rotation in Pathology lab
6. Enrollment in Ultrasound training course
7. Enrollment of subjects
8. Preliminary Photon Migration Data on Neoadjuvant Chemotherapy subjects

REPORTABLE OUTCOMES

Due to this Career Development Award I was able to generate several additional projects and obtain funding:

1. Grants

A) *ANGIOGENESIS IN HYPERPLASIA TO IN-SITU BREAST CANCER*

9WB-0020 Su (Hsiang co-PI)	7/1/2003 to 6/30/2005
California BCRP	\$250,000 Total

B) *NITRO grant: "A Network for Translational Research in Optical Imaging: Multi-Dimensional Diffuse Optical Imaging in Breast Cancer*

CA-03-002 Tromberg (Hsiang co-PI)	9/1/2003 to 8/31/2008
National Institute of Health	\$7.1 million Total

2. Presentations

- 2003 Jakubowski D.B., Cerussi A.E., Bevilacqua F., Shah N., Tromberg B.J., **Hsiang D.**, Butler J., and Holcombe R.F., "Monitoring breast tumor response to chemotherapy with broadband near-infrared tissue spectroscopy," *Spring Topical Meeting, Optical Society of America, Biomedical Optical Spectroscopy and Diagnostics*, Miami, FL, Presentation TuB5
- 2002 **Hsiang D.**, Cerrussi A., Jakubowski D., Baick C., Tromberg B., and Butler J. "Monitoring the response of breast cancer tumors to chemotherapy with photon migration spectroscopy" *American College of Surgeon, Southern California Chapter*, Santa Barbara, CA Presentation

3. Papers

- 2004 Jakubowski D.B., Cerussi A.E., Bevilacqua F., Shah N., **Hsiang D.**, Butler J., and Tromberg B.J., "Monitoring neoadjuvant chemotherapy in breast cancer using quantitative diffuse optical spectroscopy: a case study", *Journal of Biomedical Optics*, 9(1), 230-238 (2004).

4. Collaborations

A) **Update** – I am currently collaborating with the Epidemiology Division at UCI in submitting a Project Program Grant (PPG) for Evaluating High Risk Breast Cancer Women. There is a total of 4 projects in this grant. I am the Principle Investigator on Project 3. (Breast Tissue Optical Properties by Laser Emission Skin Scanner : Project 3 of PPG Etiology and Detection of Breast Cancer in a Family Cohort - Estimate 3-4 Million for PMS section - Total PPG 12 Million). I am going to use the Photon Migration Spectroscopy (PMS) to evaluate the physiological changes in 400 high risk women over a 5 year period. This project would be correlated with the other projects looking at molecular markers and mammographic density. We had our first site visit in January 2003. The score for Project 3 was 1.7 and 2.1 for the other 3 sections (the lower the score the better) . As you can see the PMS portion received the highest score. Unfortunately, the PPG was not funded. We have resubmitted and will have another visit on June 29 2004. Hopefully the other projects will be able to get better scores. The plan is that if the PPG fails again, I am going to submit Project 3 as a RO1 grant to NIH

B) **Update** - In March 2003 I have also started a collaborative project with UCSF by using the Photon Migration Spectroscopy concurrently with MRI scanning of subjects undergoing Neoadjuvant chemotherapy. We are sharing information and there has been very exciting data generated from this collaboration. Thus far the correlation data seems to match up.

CONCLUSIONS

In summary, I feel the career development grant is proceeding very well. It has provided me with support by which I have been able to obtain other grants and collaborate with other investigators. This is shown by the 9WB-0020 Angenosis In Hyperplasia To IN-SITU Breast Cancer grant and the larger CA-03-002 NITRO grant: "A Network for Translational Research in Optical Imaging: Multi-Dimensional Diffuse Optical Imaging in Breast Cancer" grant. This would have been impossible if I did not receive this career grant. The protected time has been invaluable. It has allowed me the time to concentrate on this project and make sure everything is progressing as planned. I am happy to report that the Photomedicine division is now the highest funded division in the Department of Surgery and is one of the highlighted research projects at the Chao Family NCI Comprehensive Cancer Center.

The PMS data thus far have been fantastic. PMS has been able to measure physiological changes during the neoadjuvant treatment. As pointed out earlier, it is the early portion, for example first week that is most important. This is where we see the largest change with PMS. The ideal situation would be that PMS will be able to identify early physiologic changes in the treatment cycle and hence become a predictor of identifying the responders from non-responders. This will be come more important because the shift for chemotherapy regiments is to move to shorter time intervals. This is seen in newer protocols incorporating "Dose Dense " components into their regiments. If this shorter interval cycle proves to be a better method of delivering chemotherapy then there will be a critical need for an ultra fast measurement of chemotherapy response. The traditional methods will be too slow.

As with any new modality we are still constantly trying to verify our measurements .The project with UCSF have been encouraging in that the PMS measurements have been correlating with the MRI structural information.

Everyday we are finding new uses for the PMS laser. I am starting collaborations with Pediatrics (to non-invasively measure the hemoglobin in neonates) and Trauma (to monitor physiological parameter changes in critical patients)to find uses for the PMS laser.

I look forward to next year's final report in Philadelphia.

Appendix A

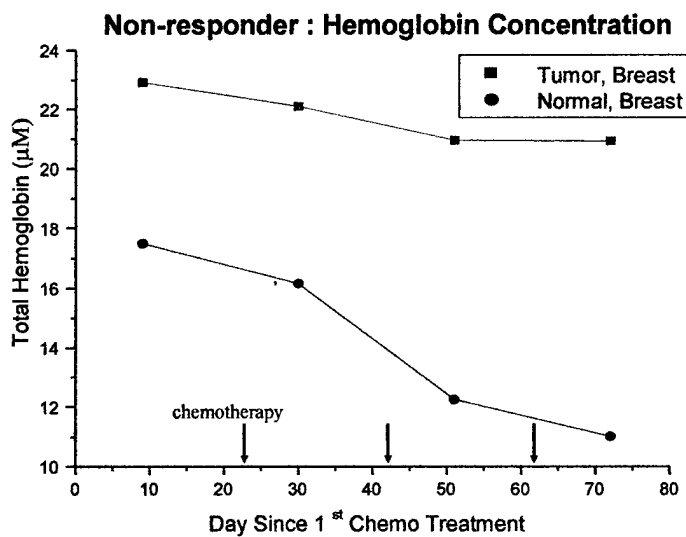
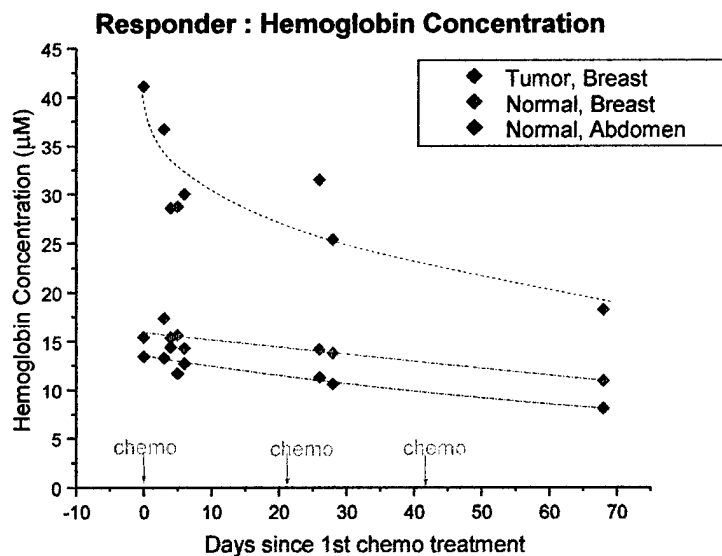
SID	MR#	Initial	Race	BD	Consent	and measurement
1	1725549	CK	asian	10/5/1954	6/18/2002	6/24,27 - 7/3,8,29 - 8/14,20 - 9/16
2	1728491	RK	asian	1/20/1947	7/19/2002	7/31-8/5,9,15,21-9/4,11,18,25-10/2,9,17,24,31-11/14,21,12,11,19-1/9/03,2/27/03
3	1742493	SV	asian	7/10/1949	8/23/2002	9/4,10,19,25-10/1,10,17,31-11/7,21-12/5,10,23-1/13/03,2/19/03
4	1658696	SA	islander	6/19/1955	11/19/2002	11/16-12/10,20-1/8/03,15,22,31-2/6,12,19-3/7-19-26,4/2,9,16-5/21
5	1753460	RV	hispanic	10/29/1937	12/4/2002	12/11,13,16,19,23-1/8/03,15,23,30-2/5,12,19-3/7,18,26-4/9,16-5/21
6	1759566	AS	hispanic	10/23/1969	12/4/2002	12/18,23-1/8/03,15,22-2/5,12,19-3/7,19,26-4/2,16-5/16,27-6/13-7/18,22
7	1759577	MG	hispanic	3/14/1964	12/5/2002	withdrawn from the study
8	1759670	OG	hispanic	5/2/1972	12/11/2002	1/8/03,9,14,17,21,31-2/4,11,19,27-3/7,19,26-4/16,24-5/7,16,21,27-6/5,27
9	1792490	VH	white	3/25/1946	7/16/2003	7/17,18,30,31-8/15,18-9/26-10/3,17,31-11/17-12/3-1/9/04
10	1728002	JR	asian	1/12/1964	7/16/2003	7/28,29-8/7,11,21,25-9/4,10,18,25-10/2,6,16,20
11	1794682	EH	hispanic	9/26/1960	7/23/2003	withdrawn from the study
12	1811544	MC	hispanic	3/2/1972	9/22/2003	10/1,2,3,9,23-11/6,13,17,26-12/1,9,15-1/9/04,2,18
13	1813315	DR	white	11/4/1953	10/20/2003	10/22,23,24,11/4,12,17,12/8,15,1/5/04,12,21,26,2/2,9,13,19,25,3/3,8,15,22,31,4/5,12,19,27
14	1824608	CB	black	6/15/1969	1/7/2004	2/5,13,17,18,19,25 3/10,17,24,31,4/22,28,5/5
15	1833152	SC	asian	4/9/1957	2/2/2004	withdrawn from the study
16	1797822	OA	white	2/9/1940	2/27/2004	3/1,2,3,11,17,26,31,4/9,15,22,29,5/7
17	18438291	MN	white	8/9/1944	4/20/2004	4/27,28,29,30, 5/3
18	1810529	MR	hispanic	5/21/1963	4/22/2004	4/28,30,5/5
19						
20						

Appendix B

SS	date	position	water	fat	HbO2	Hb-R	THC	StO2	Scatter Power	profit	residual	TOI	OX/DX
		left01	14.63823	92.84946	6.709457	4.938901	11.64836	57.60345	-0.854325233	179.1996	0.003411	0.031881	1.358492
03.07.20		left02	15.62955	88.26139	11.3495	6.636018	17.98551	62.76163	-0.7960762	130.786	0.003783	0.050746	1.710287
03.07.20		left03	17.46477	86.75188	10.30696	6.546994	16.85395	60.64374	-0.860859295	212.8488	0.004351	0.05595	1.574304
03.07.20		left04	17.63983	50.81534	8.424872	5.661419	14.08629	59.79613	-1.153767871	1366.18	0.003593	0.081775	1.48812
03.07.20		left05	19.59119	51.41478	8.463857	7.361495	15.82535	53.52544	-0.902843302	260.9847	0.003817	0.112659	1.149747
03.07.20		left06	28.34707	79.05694	15.97221	7.503795	23.47601	67.92758	-1.28609688	4294.3	0.005082	0.123921	2.128551
03.07.20		left07	29.75289	89.51375	15.98926	8.562045	24.5513	64.98803	-0.820935105	149.5275	0.003729	0.125568	1.867458
03.07.20		right01	10.01373	79.72811	5.750354	3.514117	9.264471	60.82192	-0.474374961	12.3699	0.003407	0.019131	1.636358
03.07.20		right02	9.83932	74.71562	5.90725	3.513991	9.42124	62.44669	-0.480616988	13.53645	0.003333	0.019868	1.681066
03.07.20		right03	9.726514	75.94542	7.799126	3.937521	11.73665	65.88075	-0.459050483	11.53232	0.003636	0.022816	1.98072
03.07.20		right04	10.02557	81.32715	5.645511	3.570828	9.216339	61.15298	-0.484128242	15.92117	0.002789	0.018579	1.581009
03.07.20		right05	9.486455	75.43291	7.562839	4.039736	11.60258	64.38047	-0.386468342	7.578081	0.00347	0.022664	1.872112
03.07.20		right06	9.541892	74.68658	6.1492	3.767904	9.917104	61.96867	-0.367794226	6.903009	0.002965	0.020446	1.631995
03.07.20		right07	10.15334	74.36012	8.987594	4.445216	13.43281	66.66193	-0.437716057	12.32353	0.003768	0.027514	2.021857
03.07.20		abd	12.99203	81.95087	4.95848	4.182307	9.140787	53.90692	-0.663998626	57.26602	0.003161	0.026882	1.185585
03.07.31		left01	9.953086	55.08017	9.917101	3.668324	13.58542	72.94396	-0.791089982	297.6162	0.002783	0.033655	2.703442
03.07.31		left02	10.13354	47.95181	9.416536	3.889649	13.30619	70.83988	-0.861344371	451.1804	0.002387	0.039695	2.420922
03.07.31		left03	11.29527	50.09957	9.654955	4.063632	13.71859	70.36727	-0.894656169	549.6846	0.002175	0.043954	2.375942
03.07.31		left04	11.88642	56.36981	10.85157	4.106627	14.9582	72.46897	-0.888163597	587.4789	0.002358	0.043524	2.642453
03.07.31		left05	11.80449	48.68568	9.823068	3.872414	13.69548	71.73446	-0.893262568	881.7354	0.002114	0.046291	2.536678
03.07.31		left06	13.2153	48.14126	10.03663	3.750847	13.78748	72.75438	-0.929133125	666.7876	0.002145	0.052022	2.675831
03.07.31		left07	16.24316	50.85766	12.14824	4.039346	16.18758	74.95098	-1.087111943	1958.556	0.002871	0.068979	3.007476
03.07.31		right01	11.20145	81.35007	6.410182	3.591623	10.00181	64.10056	-0.546798755	20.61666	0.002933	0.021485	1.784759
03.07.31		right02	11.76811	75.69437	7.265233	4.545791	11.81102	61.46164	-0.552412198	23.90879	0.003245	0.029876	1.598233
03.07.31		right03	11.49204	76.86352	3.739685	4.119095	7.85878	47.50043	-0.456433614	11.52627	0.002542	0.024736	0.90789
03.07.31		right04	13.13396	76.37928	5.863583	5.029459	10.89304	52.72157	-0.665451285	51.34047	0.003148	0.035529	1.165848
03.07.31		right05	13.05324	77.56917	5.337129	4.514591	9.85172	49.62161	-0.671299981	52.95239	0.003161	0.03341	1.182195
03.07.31		right06	13.49204	74.91441	6.144984	5.164948	11.30993	53.67544	-0.680835578	53.90645	0.003407	0.037949	1.189747
03.07.31		right07	12.22698	76.80633	7.001132	4.505023	11.50615	58.85594	-0.619374795	34.02153	0.003266	0.031122	1.554072
03.07.31		abd	12.26923	82.01241	6.395769	3.027954	9.423723	67.58367	-0.707056397	80.9035	0.002887	0.02086	2.112241

Appendix B

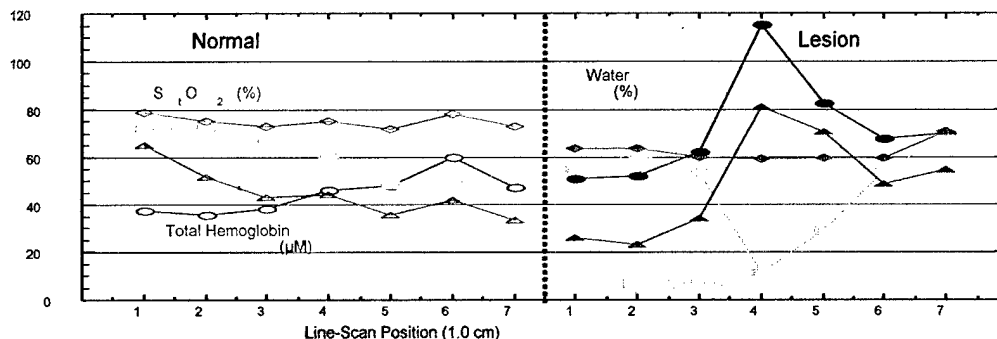
Example of hemoglobin change with time course of chemotherapy



Appendix C

Optical Index

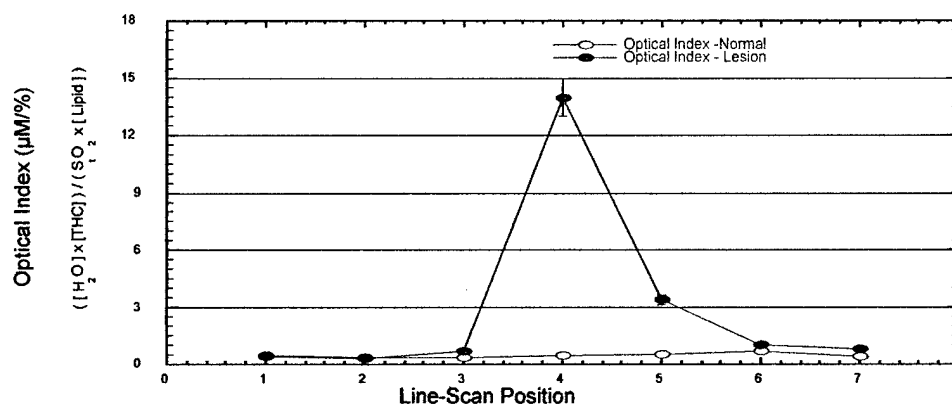
An index was created to simplify the interpretation of the multiple parameters obtained on the tumor. Below is an example.



As one can see there are several plotted data lines which can be confusing any distracting.

As a result we decide to create an index:

$$\text{Total Optical Index} = \frac{\text{Total Hemoglobin} \times \text{Water (H}_2\text{O)}}{\text{Lipid} \times \text{Oxygen Saturation (S}_t\text{O}_2)}$$



With this index it is easier to locate the peak value for the tumor and when plotting it is simpler to use the peak TOI (total optical index). Now whether this is the final form of the index has not been determined. The issue will be discussed with a mathematician on main campus.